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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
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NEW DELHI - 110 008.

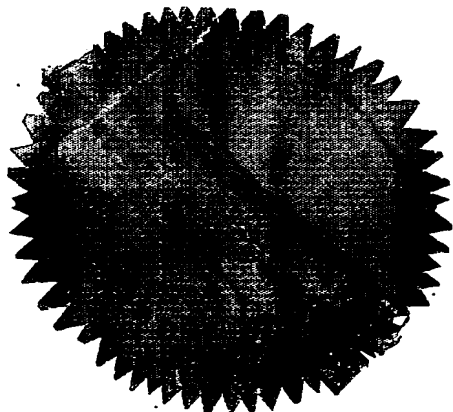
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*I, the undersigned being an officer duly
authorized in accordance with the provision of the
Patent Act, 1970 hereby certify that annexed hereto is
the true copy of the Application, Complete
Specification and Drawing Sheets filed in connection
with Application for Patent No. 1306/Del/2003 dated
22nd October 2003. ✓*

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Witness my hand this 10th day of February 2005.



(S.K. PANGASA)

Assistant Controller of Patents & Designs

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1. We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India
2. hereby declare –
- (a) that we are in possession of an invention titled **"AN IMPROVED PROCESS FOR THE PREPARATION OF CEFTRIAXONE"**
- (b) that the Complete Specification relating to this invention is filed with this application.
- (c) that there is no lawful ground of objection to the grant of a patent to us.
3. Further declare that the inventors for the said invention are
- a. YATENDRA KUMAR
 - b. NEERA TEWARI
 - c. BISHWA PRAKASH RAI
 - d. HASHIM NIZAR POOVANATHIL NAGOOR MEERAN
 - e. RAM CHANDER ARYAN
- of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.
4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **INDIAN PATENT APPLICATION NO.493/DEL/2001 FILED ON 17.04.2001.**
5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**
6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on Under section 16 of the Act. **NOT APPLICABLE**
7. That we are the assignee or legal representatives of the true and first inventors.
8. That our address for service in India is as follows:
- DR. B. VIJAYARAGHAVAN**
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001-10; 5012501-10

9. Following declaration was given by the inventors or applicants in the convention country:

We, YATENDRA KUMAR, NEERA TEWARI, BISHWA PRAKASH RAI, HASHIM NIZAR POOVANATHIL NAGOOR MEERAN, RAM CHANDER ARYAN of Ranbaxy Laboratories Limited, Plot No. 20, Sector - 18, Udyog Vihar Industrial Area, Gurgaon-122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

Neera Tewari
(NEERA TEWARI)

c.

Bishwa
(BISHWA PRAKASH RAI)

d.

Hashim Nizar
(HASHIM NIZAR POOVANATHIL NAGOOR MEERAN)

e.

Ram Chander Aryan
(RAM CHANDER ARYAN)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on the application.

11. Followings are the attachment with the application:

- Complete Specification (3 copies)
- Drawings (3 copies)
- Priority document(s)
- Statement and Undertaking on FORM - 3
- Power of Authority (Not required)
- Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 22ND day of October, 2003.

For Ranbaxy Laboratories Limited

Sushil Kumar Patawa
(SUSHIL KUMAR PATAWA)
Company Secretary

FORM 2

1306 DEL 03

The Patents Act, 1970
(39 of 1970)

22 OCT 2003

COMPLETE SPECIFICATION
(See Section 10)

**AN IMPROVED PROCESS FOR THE
PREPARATION OF CEFTRIAXONE**

PLGAT

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

**The following specification particularly describes and ascertains the nature
of this invention and the manner in which it is to be performed:**

The present invention relates to a cost effective and commercially viable process for the preparation of ceftriaxone at an industrial scale.

Chemically, ceftriaxone is $[(6R-[6\alpha,7\beta(Z)])-7-[2-(2\text{-aminothiazol-4-yl})-2\text{-methoxyimino)acetamido}]-3-[[[(2,5\text{-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thio]methyl}]-3\text{-cephem-4-carboxylic acid}]$ having Formula I, as shown in the accompanied drawings and is known from the US Patent No. 4,152,432. Ceftriaxone sodium is a semisynthetic, broad-spectrum cephalosporin antibiotic for parenteral administration characterized by activity against gram-positive and gram-negative microorganisms.

Several general processes are known for the preparation of cephalosporin antibiotics viz., US 4,409,215, US 5,109,131, GB 2012276 and WO 00/63214. However, attempts for extending these processes for preparing ceftriaxone at an industrial scale did not give desired results with respect to yield and quality. More particularly, the synthetic process comprising coupling of reactive acid derivative of compound of Formula II, as shown in the accompanied drawings, with reactive derivative of an open chain compound of Formula III, as shown in the accompanied drawings, wherein X is a halogen selected from chloro, bromo and iodo, to get a compound of Formula IV, as shown in the accompanied drawings, and its subsequent cyclization with thiourea to obtain ceftriaxone of Formula I was found to be unsatisfactory at a commercial scale. Processes cited in US 4,409,215 and GB 2012276 require protection at the carboxylic position of the compound of Formula II followed by the steps of coupling and cyclization as described above. The product obtained is then subjected to hydrolysis to get ceftriaxone. The additional steps of protection and deprotection result in low yields and cost escalation. The processes cited in WO 00/63214 and US 5,109,131 require formation of compound of Formula IV as above and its subsequent cyclization with thiourea in a mixture of organic solvent and water to afford ceftriaxone. Ceftriaxone thus obtained is of poor quality.

Hence, none of the processes heretofore described are completely satisfactory for various reasons.

The present invention provides a process for the preparation of ceftriaxone of Formula I, or a pharmaceutically acceptable salt thereof, which involves simple operations and gives good yields and high purity (99%) by HPLC.

In particular, the present invention provides a process for the preparation of ceftriaxone of Formula I, as shown in the accompanied drawings, or a pharmaceutically acceptable salt thereof, comprising:

- (i) reacting a compound of Formula V, as shown in the accompanied drawings, wherein R is hydrogen or a silyl group and R' is a silyl group or COOR' is a carboxylic acid salt, with a compound of Formula III, as shown in the accompanied drawings, or its reactive acid derivatives, wherein X is a halogen, to obtain a compound of Formula VI, wherein X and R' are as defined above,
- (ii) desilylating or acidifying the compound of Formula VI, and
- (iii) reacting the compound of Formula IV obtained from the above step with thiourea in aqueous medium in the presence of a weak base to obtain ceftriaxone of Formula I, which may be converted into its salts.

Carboxylic acid salts of compound of Formula V include salt with a metal such as sodium or potassium, or salt with an organic amine such as triethylamine, pyridine, dicyclohexylamine or N, N-dimethylaniline.

R and R' in the compound of Formula V may be silyl groups which may be the same or different. Suitable silyl groups are trialkyl silyl groups wherein the alkyl substituents may be the same or different. Preferred alkyl substituents are methyl, ethyl, isopropyl and tert-butyl. Preferred silyl groups are trimethylsilyl and tert-butyl dimethylsilyl.

X in the compounds of Formula III, IV and VII is a halogen selected from chloro, bromo and iodo. X is preferably bromo.

Reactive acid derivatives of the compound of Formula III include the acid halides, the acid anhydride, mixed acid anhydrides, reactive esters, reactive amides and the acid azide. Preferred mixed acid anhydrides include anhydrides with lower alkanolic acids

such as pivalic acid, trichloroacetic acid or anhydride with a carbonic acid such as monomethylcarbonate. Preferred reactive esters include p-nitrophenylester, N-hydroxysuccinimido ester, N-hydroxyphthalimido ester, 2-mercaptobenzothiazolyl ester and 2-mercapto-5-methyl-1,3,4-thiadiazolyl ester. Among the reactive acid derivatives of Formula III, acid halides are preferred.

When the compound of Formula III is employed in the form of a free acid, the reaction step (i) is carried out in the presence of a condensing agent such as dicyclohexylcarbodiimide or a Vilsmier reagent which may be prepared for example from dimethylformamide and phosphorous oxychloride.

Where a reactive derivative of the acid of Formula III is employed, the use of such a condensing agent is not required, however, it may be desirable to carry out the reaction in the presence of a base which may be an alkali metal compound such as sodium bicarbonate, sodium carbonate and potassium carbonate, or an organic amine such as triethylamine, lutidine and pyridine.

The reaction of step (i) is usually conducted in a suitable solvent. When R, R' or both are silyl in the compound of Formula V, suitable solvents for the reaction include halogenated hydrocarbons such as methylene chloride, hydrocarbons such as toluene, ethers such as tetrahydrofuran or polar solvents such as dimethylformamide, or a mixture thereof. When R is hydrogen and COOR' is a carboxylic acid salt in the compound of Formula V, suitable solvents for the reaction include methanol, ethanol, acetonitrile, dimethylformamide, water, or a mixture thereof.

The starting compounds of Formula V wherein R, R' or both are silyl may be obtained by silylating the corresponding 7-amino-3-[[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thio]methyl]-3-cephem-4-carboxylic acid of Formula II with a suitable silylating agent. Appropriate silylating agents include halosilanes such as trimethylsilylchloride (TMCS), dimethyldichlorosilane (DMDCS), silylated amides such as N, O-bis(trimethylsilyl) acetamide (BSA), silazanes such as 1,1,1,3,3,3-hexamethyldisilazane (HMDS), silylated ureas such as N, N'-bis-(trimethylsilyl) urea (BSU), or a mixture thereof

Where COOR' is a carboxylic acid salt in the compound of Formula V, it may be obtained in a conventional manner, for example by treatment of compound of Formula II with a base such as sodium bicarbonate, triethylamine etc.

Compounds of Formula II and III may be obtained by methods known in the art.

Desilylation (Step ii) of a compound of Formula VI (wherein R' is a silyl group) may be carried out according to conventional methods such as treatment with methanol / water to isolate compound of Formula IV.

The reaction of a compound of Formula IV with thiourea is carried out in the presence of a weak base such as sodium acetate and sodium bicarbonate in water. Compound of Formula IV is added to aqueous solution of the weak base at a temperature of about 0 to 15°C. Thereafter, an aqueous solution of thiourea is added to the above mixture at a temperature of about 0 to 15°C. The reaction may then be carried out a temperature of about 0 to 60°C, preferably at 0-25°C, more preferably at 10-20°C. Ceftriaxone of purity 99% is obtained after acidifying the aqueous layer to a pH of about 2.5 to 3.

Ceftriaxone so obtained may be converted to ceftriaxone salts by methods known in the art such as reaction with sodium acetate in aqueous acetone to get ceftriaxone sodium.

In the following section a preferred embodiment is described by way of example to illustrate the process of this invention. However, it is not intended in any way to limit the scope of the present invention.

EXAMPLE

Preparation of ceftriaxone disodium

- (i) 7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]-3-[[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl]thio]methyl]-3-cephem-4-carboxylic acid

Solution A

Hexamethyldisilazane (12.7g) and acetamide (21.6g) were refluxed in dichloromethane (160ml) in the presence of a catalytic amount of imidazole (0.2g) for two hours. The mixture was cooled to 20 to 25°C and 7-amino-3-[[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (20.0g) was added to the resulting solution and refluxed for 1 hour to obtain almost a clear solution. The solution was cooled to 0 to -5°C.

Solution B

Phosphorous pentachloride (12g) was added to a solution of 4-bromo-2-methoxyimino-3-oxobutyric acid (12.6g) in dichloromethane (160 ml) at about -20 to -10°C and stirred for about one hour at the same temperature. The mixture was cooled to -60 to -65°C and acetamide (9.7g) was added.

Solution A was added to solution B at about -65 °C and the temperature was slowly raised to -15 to -10°C in 40 minutes. The mixture was further stirred at about -15 to -10°C for 30 minutes. The reaction mixture was then poured into a mixture of water (200 ml) and methanol (50 ml). The organic layer was separated and stirred with a solution of sodium bicarbonate (20g) in water (300ml). The aqueous layer was separated.

- (ii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (ceftriaxone)

A solution of thiourea (5.0g) in water (50 ml) was added to the aqueous layer from from step (i) above. The mixture was stirred at 20 to 25°C for about one hour. Reaction mixture was then treated with activated carbon (2.0g) for 15 minutes, filtered, washed with water and pH of the aqueous layer was adjusted to about 2.5 to 2.8 with 6N hydrochloric acid. The mixture was cooled to 0 to 5°C and stirred for one hour to obtain ceftriaxone (18 g; purity by HPLC = 99%) after filtration and drying at 45-50°C.

- (iii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid, disodium salt (ceftriaxone disodium)

WE CLAIM :

1. A process for the preparation of ceftriaxone of Formula I as shown in the accompanied drawings, or a pharmaceutically acceptable salt thereof, comprising
 - (i) reacting a compound of Formula V, as shown in the accompanied drawings, wherein R is hydrogen or a silyl group and R' is a silyl group or COOR' is a carboxylic acid salt, with a compound of Formula III, as shown in the accompanied drawings, or its reactive acid derivatives, wherein X is a halogen, to obtain a compound of Formula VI, wherein X and R' are as defined above,
 - (ii) desilylating or acidifying the compound of Formula VI, and
 - (iii) reacting the compound of Formula IV obtained from the above step with thiourea in aqueous medium in the presence of a weak base to obtain ceftriaxone of Formula I, which may be converted into its pharmaceutically acceptable salts:
2. The process of claim 1 wherein both R and R' are trimethylsilyl in the compound of Formula V, as shown in the accompanied drawings.
3. The process of claim 1 wherein X is chloro or bromo in the compound of Formula III.
4. The process of claim 1 wherein the reactive derivative of Formula III is the acid chloride.
5. The process of claim 1 wherein the reaction of step (iii) is carried out in the presence of sodium acetate or sodium bicarbonate as the weak base.
6. The process of claim 1 wherein in step (iii), compound of Formula IV is added to an aqueous solution of sodium acetate or sodium bicarbonate at a temperature of about 0 to 15°C.

Ceftriaxone (30g) was suspended in water (150ml) at 0 to 5°C, and triethylamine (10g) was added to it at the same temperature in 15 to 20 minutes. The solution was treated with activated carbon (6g) for 30 minutes, filtered and washed twice with water (30ml each). Solution of sodium 2-ethylhexanoate (21g) in acetone (60ml) was added to the combined filtrate at 15 to 20°C. The mixture was stirred for 20 minutes at 4 to 5°C, acetone (360ml) was added slowly, followed by seeds of ceftriaxone disodium and the stirring continued at the same temperature for 15 minutes. Acetone (540ml) was added in 60 to 80 minutes at 15 to 20°C and the stirring further continued at the same temperature for 15 minutes to obtain ceftriaxone disodium (25.8g; purity by HPLC = 99%) after filtration and drying at 40-45°C.

7. The process of claim 1 wherein in Step (iii) thiourea is added at a temperature of about 0 to 25°C.
8. The process of claim 1 wherein the reaction of step (iii) is performed at a temperature of about 10 to 30°C.
9. The process of claim 1 wherein ceftriaxone is isolated at a pH of about 2.5 to 3.0.
10. The process for the preparation of ceftriaxone of Formula I, as shown in the accompanied drawings, or a pharmaceutically acceptable salt thereof, as herein described and exemplified by the example.

Dated this 22ND day of October, 2003.

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

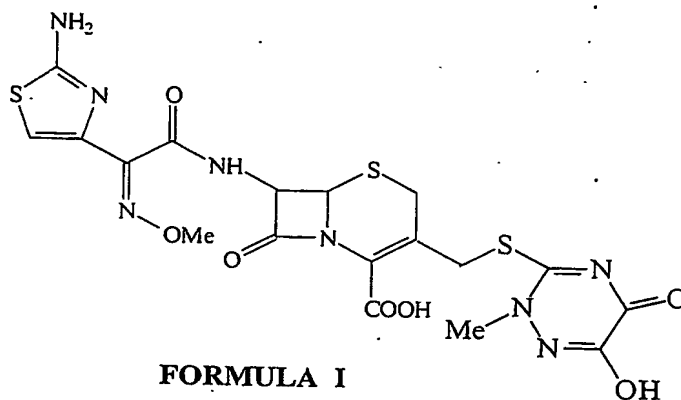
Ranbaxy Laboratories Limited

Application No.

No. of sheets = 06

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For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

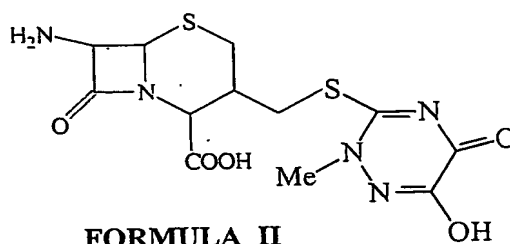
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FORMULA II

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

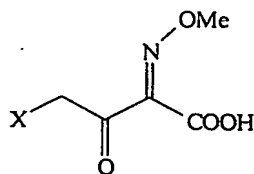
Ranbaxy Laboratories Limited

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No. of sheets = 06

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1506-03



FORMULA III

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

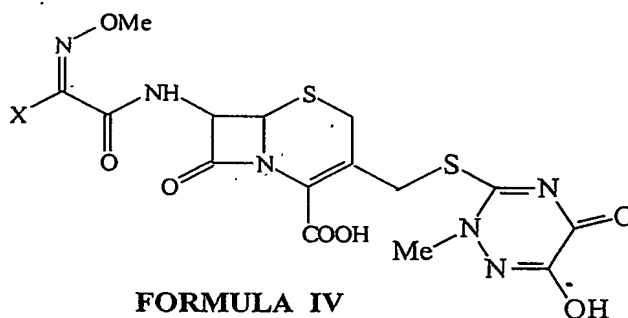
Ranbaxy Laboratories Limited

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Application No.

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1306-03



FORMULA IV

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

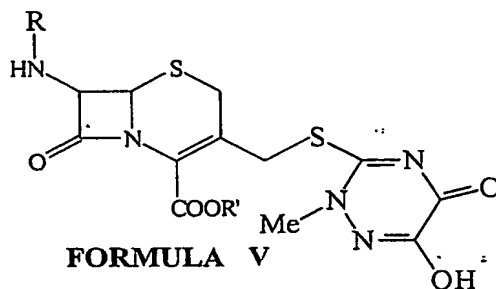
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Application No.

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For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

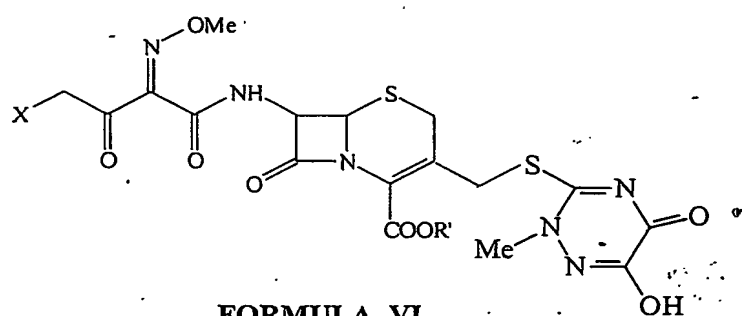
Ranbaxy Laboratories Limited

No. of sheets = 06

Application No.

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1506-03



FORMULA VI

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

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